GLOBAL MEDICAL ETHICS

Xenotransplantation: a bioethical evaluation

M Anderson

J Med Ethics 2006;**32**:205–208. doi: 10.1136/jme.2005.012914

Allograft shortage is a formidable obstacle in organ transplantation. Xenotransplantation, the interspecies transplantation of cells, tissues, and organs, or ex vivo interspecies exchange between cells, tissues, and organs is a frequently suggested alternative to this allograft shortage. As xenotransplantation steadily improves into a viable allotransplantation alternative, several bioethical considerations coalesce. Such considerations include the Helsinki declaration's guarantee of patients' rights to privacy; political red tape that may select for undermined socioeconomic groups as the first recipients of xenografts; industry incentives in xenotransplantation investments; conflicts of interest when a clinician supervises a patient as a research subject; the psychosocial impact of transplantation on the xenograft recipient, and the rights of animals. This review illuminates these issues through a conglomeration of expert opinion and relevant experimental studies.

The number of individuals waiting for an allotransplant in the United States is steadily increasing, without proportional increases in viable donated organs. Presently, nearly half of those needing an organ transplant will die waiting.[1] Health education and organ donation encouragement are suggested as important, non-invasive measures to circumvent this organ shortage problem.[2] Despite knowledge dissemination efforts, however, the shortage of allografts remains a formidable obstacle to organ transplantation. Efforts to broaden the organ base include ''presumed consent''—that is, assuming that a dying person donates their organ unless otherwise stated—and offering financial incentives for organ donation. Both of these practices are regularly implemented in Europe. A more extreme option, which is common in China, is for the highest bidders to receive organs from prisoners who did not consent to their organs being transplanted.[1] Executions are scheduled to coincide with transplantations and conducted in such a way that the organ is most viable. The United States is hesitant to adopt any of these practices, as doing so may marginalise the value of a human life. Further, neither ''presumed'' consent nor financial incentives have resulted in appreciable increases in donated organs.[1 3]

Xenotransplantation, defined as the interspecies transplantation of living cells, tissues, and organs, or ex vivo interspecies exchange between living cells, tissues, and organs, is a frequently mentioned alternative to the organ shortage problem. It is difficult to delineate the history of xenotransplantation as its beginnings are somewhat blurred. As insightfully put by Melo *et al*[4]: ''After all, was not Daedalus, a man who grafted bird feathers to his arms so that he could escape from his island prison in Crete and fly to the mainland of Greece, probably the first recipient of a xenotransplant that was successful?'' Although haphazard experimental and clinical xenotransplants were regularly conducted at the turn of the 20th century—for example, cross clinical implantation of kidneys between rabbits, goats, lambs, and non-primate human donors[5]—sophisticated studies of xenografts were not initiated until the 1960s. In 1964, Reemstma[6] transplanted a chimpanzee kidney into a human with end stage renal disease, extending the participant's life a record nine months. Despite medical science's considerable improvements in immunosuppressive therapy, xenograft survival times remain a modest few months at best.[7]

Daar *et al*[3] mention that, with few alternatives to the allograft shortage, there is a '' time to put man on the moon'' renewed enthusiasm about the prospects of xenotransplantations. Should the potential of this procedure be realised, relevant ethical, public policy, economic, psychosocial, and animal rights considerations must be addressed. It is the objective of this review to highlight these issues.

ETHICAL CONSIDERATIONS

Although progress in tissue modification techniques continues to extend the life of a xenograft, long term graft acceptance is far from realisation. When present research efforts do culminate in a long term solution to organ shortage, the risk of infectious disease transmission must be addressed. The cloud of immunological rejection itself is silver lined with the decreased risk of viral admittance into a particular host. Lowering defence barriers through immunosuppressant therapeutics and morphing phylogenetically distant organs to grafts recognised as ''self'' by a human recipient may open the way for the emergence of new viral mosaics into the general population. Containment of this infectious risk calls for ethically debatable measures.

Tissue samples from the donor animal must be carefully screened for known pathogens and archived to test for pathogens of which health professionals are not yet aware. Error in testing

Correspondence to:
M Anderson, University of North Carolina at Charlotte, 12617 Netherhall Dr, Charlotte, NC 28269, USA;
mganders@uncc.edu

Received 18 May 2005
Accepted for publication 2 July 2005

Abbreviations: HPC, hepatitis C; IACUC, Institutional Animal Care and Use Committees; IRB, institutional review board; NOTA, National Organ Transplant Act; RAC, Recombinant DNA Advisory Council

accuracy must be considered, especially in light of a hepatitis C (HPC) outbreak in 2000.[8] The donor of this allotransplant erroneously tested HPC negative, allowing the pathogen to infect eight of the 40 transplant recipients. In retrospect, the donor probably had not developed an antibody response sufficient for titre detection. Because of testing imperfection such as this, serum samples from xenotransplant recipients must be taken before, and regularly after, the transplantation. Further, epidemiologists recommend an international registry of xenotransplant recipients with associated lifetime surveillance, as a public health precaution.[1] Such monitoring may even be extended to the sexual partners, friends, and family of recipients.[9]

Mandatory surveillance such as this is ethically controversial, as doing this violates rights to individual privacy. Precedents, such as the Declaration of Helsinki and the Nuremberg trials declaration, ensure that participation in studies is entirely voluntary, not hurried, and exit from the study is the autonomous decision of each participant. Although xenotransplant recipients are free to leave a particular study, most of the medical community deems mandatory clinical monitoring surveillance necessary to limit infectious spread. The problem of maintaining ethical standards in situations such as this is vexing. Welin and colleagues[10] cite a statement from the Nuffield Council on Bioethics[11]: ''It would hardly be ethical to isolate xenograft recipients suffering from an infectious disease, or to ask them to refrain from sexual intercourse or…from having children.''

PUBLIC POLICY AND ECONOMIC CONSIDERATIONS

Protection of public health from the infectious risk of xenotransplantation requires cooperation among national and international agencies. Although the World Health Organization (WHO) recently convened to assess the infectious risk of xenotransplantation, no consensus on how trials should be conducted and monitored was reached.[12] Presently, the only national protocol for third party risks in the United States is that of the Food and Drug Administration's Recombinant DNA Advisory Council (RAC).[1] Guidelines set by the RAC are negotiable at a municipal level, as demonstrated by resistance of the citizens of Cambridge, Massachusetts to the Institutional Review Boards (IRB) and the Institutional Animal Care and Use Committees (IACUC), which approved gene recombination studies at Harvard and the Massachusetts Institute of Technology (MIT).[1] A town council meeting, composed entirely of non-scientists, approved the research, although not without stipulations of continued citizen approval.

Although public consent for procedures placing public health at stake is necessary, this case exemplifies the potentially problematic aftermath of allocating legislative power to non-scientists on a scientific matter. Bach and colleagues[13] recommend that advisory councils be constructed to voice public concerns. Such councils would not have direct legislative authority over the fate of research, but rather they would voice their concerns to their elected officials. In this way, both scientific and ethical perspectives would be soundly incorporated into the regulation of research.

Legislative reform at the IRB and IACUC level is also necessary to manage the myriad of ethical and scientific concerns encompassed by xenotransplantation. To fully understand the infectious and ethical risks of a particular xenotransplant trial, a variety of scientific expertise in immunology and animal microbiology is needed. Such experts may not be readily available through an IRB or an IACUC. Although industry may provide expert committees to advise on extramural funding of a particular study, if funds are denied, the study may still proceed pending IRB and IACUC approval. In addition to expanding their knowledge bases, IRBS and IACUCS must also be equipped to consider third party interests before approving studies such as xenotransplantation.

Infectious agents do not know national borders, a point stressed by the American Society of Transplant Physicians (ASTP), which feels that regulations on xenotransplant trials in the United States are not stringent enough in light of the infectious risk.[3] The ability of individuals to obtain allotransplants from live donors in impoverished countries, recently exemplified in allowing patients with hepatic failure in the United Kingdom to arrange liver transplants from the Philippines via a website, Liver4you.org,[14] calls attention to the need for global legislation on procedures that increase the risk of infections being spread internationally.

Public health advisory councils outside of the US have voiced concerns that the commercial medical industry in America may overly influence matters governed by American public health regulatory powers, as evidenced by a push for xenotransplantation trials in the United States without prudent, objective analysis of infectious risk.[3] Indeed, rapid progress in clinical xenotransplantation allows companies to quickly reallocate front end investment in research. While premature clinical application without a sound research base may benefit industry, it poses a public health risk, should widespread xenotransplantations and postoperative care outstrip necessary knowledge of zoonotic infection.

The bureaucracy involved in xenotransplantation studies is further complicated when physicians are stakeholders within the medical industry. Daar[3] cites collaboration on xenotransplantation between T-Cell Sciences Inc, Johns Hopkins and Harvard (Bringham Hospital); between Biotransplants and Cell Genesys and Harvard (Massachusetts General Hospital), and between Imutran (now part of Novartis) and Cambridge University in England.[15] Serving as both a clinician and a researcher could place one's obligation to the wellbeing of the patient in direct opposition to the advancement of academic medicine. In a worst case scenario, this role schism could lead to the urging of a patient to partake in a trial, when without such urging he or she would probably not take part. Such was the case in 1984 with Baby Fae, an infant who underwent xenotransplantation with a baboon heart. The parents of the neonate were overenthusiastically assured that ''long term survival with appropriate growth and development may be possible following heart transplantation. . .this research is an effort to provide your baby with some hope of immediate and long term survival.''[1] Baby Fae survived four weeks, as the xenotransplant research available to her physician at the time of the transplantation predicted.

It is this identity of a patient as a research subject, in conjunction with a history of misconduct in medical science as evidenced by the Nazi medical experiments and the Tuskegee syphilis study, which leaves many plausible research groups wary of participation in xenotransplantation studies. Although special interest groups often encourage women and minorities to participate in studies that affect them,[1] a general fear of exploitation looms always in the background. Many groups are concerned that because xenotransplants are notably less viable than their allotransplant counterparts, xenografts will be implanted in those who are very ill but who cannot afford an allograft.

The National Organ Transplant Act (NOTA) of 1984 sought to dissolve this disparity in socioeconomic organ allocation, a practice known as the ''green screen''. Through NOTA and the Department of Health and Human Services, the Organ Procurement and Transplant Network was established, which formulates the distribution of viable organs irrespective of recipient socioeconomic status. The network is operated by the United States Resource and Service Administration and the United Network for Organ Sharing (UNOS).[1]

Despite the passage of NOTA, monetary status is still a real obstacle for a sizeable portion of those in need of organ transplants, particularly individuals who are uninsured or underinsured. Such individuals are unlikely to be referred to a transplant centre, as a centre requires insurance or some form of collateral to cover these expensive transplantation procedures. Although the 1972 Social Security Reform Act insures Medicare coverage of kidney transplants to approximately 90 per cent of those with end stage renal disease, this is the only form of transplantation with such widespread accessibility.[1] Transplant centres cite the tremendous expense of transplantations to justify the inaccessibility to those without adequate healthcare coverage. To cover those who cannot afford transplantation, costs would need to be absorbed by the premiums of the insured. Without access to allotransplantation, the plight of those who may agree to xenotransplantation because they cannot afford any other alternative will continue.

Although organ transplants are the most expensive of all medical procedures, transplants presently consume a mere half a per cent of total healthcare expenditure in the United States.[1] This low percentage is a reflection of the relatively low frequency of the procedure due to both organ shortage and cost savings through managed health care. Should xenotransplant studies reach their widespread clinical potential, this estimate would rise to two per cent, equating to billions more in costs.[1]

Despite the humble beginnings of now successful procedures such as cardiac allotransplants,[16] the healthcare industry is hesitant to approve high risk, low reward procedures such as xenotransplantation. Some may argue that xenotransplantation will actually add to the organ shortage problem, as more people in need of an allotransplant are bridged to longer survival times through the use of xenografts.

Psychosocial factors

Progress in xenotransplantation warrants consideration of the psychosocial impact on recipients following transplantation. Teran-Escandon and colleagues[17] evaluated a variety of psychological and quality of life factors on adolescent recipients of porcine islet cells. Although some participants had erroneous, preconceived notions about the implantation of a non-human source into their bodies (one twelve year old posed the question of smelling like a pig), such notions were abandoned after the procedure. Continued psychiatric evaluations after the transplant indicate that children were pleased with the new found autonomy following porcine islet insertions. The islet cells allow finer insulin control than insulin injections alone. This pleased response positively correlated with success of the transplantation. Unlike their children, parents were somewhat ambivalent about the outcome, citing frustrations in connection with the necessary glycaemia checks following the transplant and concern about their child's autonomy. Further evaluation indicated that the concern about their child's autonomy stemmed from their adolescent's burgeoning sexual interest and fears that the autonomy allowed through porcine islet cells would enable him or her to act on that interest. If xenotransplants realise their potential as an allotransplant alternative, it is likely that more extreme psychosocial effects will be observed in whole organ transplants, considering that whole organs resonant more with the human psyche than individual cells.

The degree of public acceptance of xenotransplantation will have a direct psychosocial impact on transplant recipients. Rios and colleagues[18] found that acceptance of animal organs was seen as a viable solution to the organ shortage problems when participants viewed xenografts as being theoretically equivalent to allografts. This acceptance positively correlated with level of education and was more widely observed among younger individuals and males. Further, percentages of acceptance gathered in this study were higher than those from previous studies, indicating a growing approval in the United States for xenotransplantation. Rios *et al*[18] cite this trend in improving xenotransplant approval percentages as international in scope, as evidenced in France,[19] Sweden,[20] and Germany.[21]

Persson *et al*[22] found significant approval ratings of cellular xenotransplantation in both public and patient populations. Clinical approval correlated with approval for furthering xenotransplant research, particularly among patient populations. No significance was found in relation to waiting time for an organ and approval for xenotransplantation research, when the patient population was subdivided at the six month waiting time mark. When both groups, the general public and patients, were questioned on approval of organ or tissue xenotransplantation, however, approval notably decreased. Disapproval was also noted when groups were informed of the substantial infectious risk of xenografts relative to allografts.

Clinicians and researchers emphasise that despite these rising approval percentages for xenotransplants, it is important that the public be informed of xenotransplantation's present applicability. In short, the public should be informed that the procedure is not equivalent to allotransplantation. Some experts are concerned that overenthusiasm for the burgeoning procedure could lead to decreases in the already meagre amount of donated organs. As eloquently put by sociologist of medicine Renee Fox at the Institute of Medicine's workshop on ethics and public policy of xenotransplantation: ''We would progressively lose what is perhaps the deepest and highest symbolic moral and existential significance of organ transplantation, its gift exchange dimension. . .that the living parts of persons are offered in life or in death to known or unknown others, to our strangers and our enemies as well as to our kin, in the form of a gift beyond duty and claim, beyond reckoning and rules''.[23]

ANIMAL RIGHTS

Although not in the forefront of challenges to xenotransplantation in the United States, the use of animals in research must be considered. While few would hold the Kantian notion of animals as only means to an end, their ''rights'' as sentient beings are often absent from a priori evaluations of organ harvesting. Philosophers such as Peter Singer contend with the moral superiority of most humans to animals, but suggest that scientists and research ethicists formulate a sentient hierarchy of all life (P Singer, personal communication, 2001). For instance, according to Mukhergee,[24] ethologist Jane Goodall finds a myriad of characteristics deemed ''human like'' in animals, such as reasoning, emotion, a defined social structure, and perhaps even a propensity to love in subhuman primates—all of which are absent in anencephalic infants and severely retarded persons. Singer does not suggest that people who fall short on the personhood scale be sacrificed in the cause experimental science, but does suggest that a consideration for the sentience of beings replace staunch speciesism, which often leads to the use animals for mere academic rhetoric. Although the application of xenotransplantation in principle is far from frivolous, consideration of animal rights in the United States is not nearly as stringent as such consideration by research approval committees outside of the US .[2 3] Melo *et al*[4] propose a phylogenesis protocol of sorts, placing biological beings hierarchically, according to how far their struggle for life mirrors what we identify as human, prior to xenotransplant study approval.

Conclusion

Xenotransplantation encompasses an innumerable array of scientific and ethical complexities. Although hardly conceivable, for instance, it is possible that if the procedure were highly developed a person might consider donating an organ to a beloved pet in need.[3] This review has sought to probe the ethical, political, and psychosocial core of xenotransplantation. Although the adequate consideration of both science and ethics before proceeding in xenotransplant clinical trials presents a difficult dualism to surmount, doing so unveils a greater symbiosis between the two that exceeds the bounds of xenotransplantation.

ACKNOWLEDGEMENTS

I thank Dr Al Maisto tremendously for his unwavering encouragement and insight in this work and in life.

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